REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and the following remarks.

It is acknowledged that the foregoing amendments are submitted after final rejection. Yet, because the amendments do not introduce new matter or raise new issues, and because the amendments either place the application in condition for allowance or at least in better condition for appeal, entry thereof by the examiner is respectfully requested.

I. Status of the Claims

Claims 1-17 and 23 remain withdrawn as non-elected. With this submission, claims 18, 37, 41, 42, and 46 are amended. Claims 22, 50 and 51 are cancelled, without prejudice to or disclaimer. Claim 52 is added. Upon entry of this paper, therefore, claims 1-18, 20-21, 23, 26-28, 33-46, 49, and 52 will be pending, and claims 18, 20-21, 23, 26-28, 33, 37-46, 49 and 52 will be under consideration.

Support for these revisions can be found throughout the specification. Thus, support for "at AL163204" and "at AL163201" can be found on page 8, lines 1-4, on page 9 lines 18-21, on page 22 lines 1-12, and on page 50 (Example 1). For "mouse embryonic stem cell," see page 3, lines 17-22, page 5 lines 4-10, page 18 lines 4-18, page 27 lines 17-21, and Examples 20, 21 and 24, *inter alia*. Furthermore, support for the added "wherein" clause (claim 18) and for new claim 52 is provided by Examples 3 and 4, as well as by tables 17 and 19, for instance.

II. Rejections Withdrawn

Applicants wish to thank the examiner for withdrawing the rejection of claims under 35 U.S.C. §112 second paragraph, and 35 U.S.C. §103(a). Additionally, applicants wish to thank the examiner for withdrawing the prior objections to the claims and specification.

III. Claim Rejection- 35 U.S.C. §112 first paragraph

Claims 41 and 46 stand rejected for an alleged lack of enabling support in the specification. In particular, the Office states that the specification "does not reasonably provide enablement for method for producing embryonic stem (ES) cells from an enormous genus of

biologically distinct organisms comprising modified foreign chromosomes or fragments thereof" (Office Action, page 3). The Office admits, however, that the specification is "enabling for methods for producing a mouse embryonic stem (ES) cell comprising a modified foreign chromosome or fragments thereof" (*id.*, page 3).

Without acquiescing to these stated grounds for rejection, applicants have chosen to advance prosecution by qualifying claims 41 and 46 in terms of mouse ES cells, which should obviate the rejection. Applicants thus request withdrawal of this ground of rejection.

IV. Claim Rejection- 35 U.S.C. §103- Kuroiwa '98 in view of Kuroiwa '00, Tomizuka and Saffery

The Office Action rejects claims 18, 20-21, 26-27, 33, and 37-46 over Kuroiwa *et al.*, *NAR* 26: 3447-48 (1998) ("Kuroiwa '98"), in view of Kuroiwa *et al.*, *Nature Biotechnology* 18: 1086-90 (2000) ("Kuroiwa '00"), Tomizuka *et al.*, *Nature Genetics* 16: 133-43 (1997) ("Tomizuka"), and Saffery *et al., J. Gene Med.* 4:5-13 (2002)("Saffery"). Applicants respectfully traverse this ground of rejection.

A. Current Obviousness Standard

The Supreme Court recently reaffirmed the Graham factors for determining obviousness in KSR Int'l Co. v. Teleflex Inc. (550 U.S. 398 (2007)). The Graham factors, as outlined by the Supreme Court in Graham et al. v. John Deere Co. of Kansas City et al., 383 U.S. 1 (1966), are: 1) determining the scope and contents of the prior art; 2) ascertaining the differences between the claimed invention and the prior art; 3) resolving the level of ordinary skill in the pertinent art; and 4) evaluating evidence of secondary consideration. The Supreme Court recognized that a showing of "teaching, suggestion, or motivation" to combine the prior art to meet the claimed subject matter could provide a helpful insight in determining whether the claimed subject matter is obvious under 35 U.S.C. § 103(a), and held that the proper inquiry for determining obviousness is whether the improvement is more than the predictable use of prior art elements according to their established functions. The Court noted that it is "important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the [prior art] elements" in the manner claimed, and specifically stated:

> Often, it will be necessary . . . to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was ***an apparent reason to combine the known elements in the fashion claimed*** by the patent at issue. To facilitate review, this analysis should be made explicit.

KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 418 (2007) (emphasis added). As discussed below, the cited art cannot render the claimed invention obvious.

B. The Referenced Art Alone / in Combination Does Not Teach the Claimed Invention

The examiner is reminded that "[t]he mere fact that references *can* be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art." M.P.E.P § 2143.01(III) citing *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385, 1396 (2007) (emphasis in MPEP). Indeed, in order to properly establish a *prima facie* case for obviousness, "at least some degree of predictability is *required*." M.P.E.P. § 2143.02(II) (emphasis added).

Applicants stress that deletion of these specific areas and keeping the remaining positions are crucial for obtaining a HAC vector that, as recited, can be **transferred** to human somatic cells and **retained stably** in such cells (see specification at Examples 4, 8, 14, 18, and 21-22). To amply embody this unexpected result, applicants have added the above-mentioned "wherein" clause to claim 18. There was no suggestion anywhere in the art of record that this outcome might be occasioned by deleting either or both of a distal region within the 21q11 region of the long arm or a distal region within the 21p11 region of the short arm of chromosome 21.

The Office admits at page 9 that "neither [Kuroiwa '98, Kuroiwa '00] nor Tomizuka *et al.* teach[es] the deletion of a distal region within the 21q11 region of the long arm and/or a distal region within the 21p11 region of the short arm of the human chromosome 21." Still, the Office asserts that it "would have been obvious to modify the method for producing a human artificial chromosome vector as taught by [Kuroiwa '98 and Kuroiwa '00] and/or Tomizuka to comprise the step of deleting a distal region within the 21q11 region of the long arm and/or a distal region within the 21p11 region of the short arm of chromosome 21" (page 11).

To bolster this proposition, the Office asserts that "Saffery et al taught that such centromere-proximal deletions is a routine design when engineering human mini-chromosome vectors" (*id.*). Yet, at the time the invention was made, human chromosome 21-based HACs were not stable in cells. Instead, there were technical difficulties in obtaining the stably retained human chromosome 21-based HAC as disclosed in the present application. Accordingly, there was no metric or principle to guide "routine design" in this regard; nor was there basis for a reasonable (*i.e.,* a principled) expectation of success in finding the deletion positions as proposed.

The Saffery reference itself describes the problems associated with the production of useful and stable HECs (Saffery pages 11-12). Thus, Saffery states that there were "problems associated with the production of useful HECs arise because they are large entities and are therefore difficult to fully characterize" (page 11 in right column, last paragraph). Saffery also states that "the large size of HECs also makes them difficult to manipulate in terms of the introduction of genes and the transfer from cell to cell in an intact form" (*id.*) According to Saffery, "it is paramount to establish that a constructed HEC is fully stable both mitotically and structurally in different human cells" (page 12 in left column, last paragraph).

By virtue of these disclosures, the cited art does not validate a *prima facie* case of obviousness because no principled combination of teachings from the references in question suggests that deletion of a distal region within the 21q11 region of the long arm and/or a distal region within the 21p11 region of the short arm of the human chromosome 21 could result in a stable HAC vector. Because of the large size of these vectors, the skilled artisan also would not have known which region(s) of the HAC, if any, could be deleted to obtain a **stable** HAC.

C. Unexpected Results

Even if a *prima facie* case were assumed, applicants still would have evidenced unexpected results sufficient for rebutting that case. Specifically, applicants show that deletion of this specific area of chromosome 21 creates a HAC vector that (1) can be stably transferred to human normal fibroblasts and to human normal somatic cells other than fibroblasts (see paragraph [0151] of US 2006/0185025) and that (2) is **retained stably**, for instance, in chicken cell lines and human cell clones (Examples 4 and 18) and in human stem cells (Examples 21 and 22), *inter alia*.

These results are unexpected because, at the time the present invention was made, the prior art taught that human artificial chromosomes were ***not*** stable in mammalian cells. The Saffery reference itself supports this understanding, given its observation that, "on transfer back into CHO or human cells, mitotic **segregation was compromised** with a **high degree of variability** in the copy number of the minichromosome and **increased mitotic loss rates**" (page 10, lines 9-12). Accordingly, there was a clear prejudice in the art against transferring an artificial chromosome into mammalian cells, which in turn underscores the surprising aspects of applicants' claimed invention.

Applicants highlight these unexpected results in present claim 18, which requires that claimed "vector [to be] mitotically stable when transferred from DT40 cells to CHO cells or human cells." Furthermore, dependent claim 52 mandates that such mitotic stability persist for at least 22 divisions. As noted, the Saffery reference itself shows this stability to have been unexpected. That is, Saffery relates "[s]tability studies [that] demonstrated faithful maintenance in DT40 cells (loss rates of 0.07-0.63% per generation); however, on transfer back into CHO or human cells, mitotic segregation was comprised with a **high degree of variability** in the copy number of the minichromosome and **increased mitotic loss rates** (0.22-1.05% loss rate per generation for HT1080 and 0.79-3.01% for CHO hybrids)" (page 10; emphasis added).

For at least these reasons, the rejection of claims 18, 20-21, 26-27, 33, and 37-46 under 35 U.S.C. § 103(a) is unsustainable. Therefore, applicants request reconsideration and withdrawal of the rejection.

V. Claim Rejection- 35 U.S.C. §103 - Kuroiwa '98 in view of Kuroiwa '00, Tomizuka, Saffery and Hattori

The Office Action rejects claims 22, 28 and 49-50 over Kuroiwa '98 in view of Kuroiwa '00, Tomizuka, Saffery and in further view of Hattori *et al. Nature* 405(6784):311-319 (200)("Hattori"). Claims 22 and 50 are cancelled, mooting the rejection as to claims 22 and 50. Applicants respectfully traverse the rejection with respect to claims 28 and 49.

The Office argues that Hattori discloses nucleotide sequences of the human chromosome 21 that achieve 99.7% coverage of 21q. However, Hattori suggests nothing about deleting a distal region within the 21q11 region of the long arm and/or a distal region within the 21p11

region of the short arm of the human chromosome 21. As such, Hattori fails to cure the deficiencies of Kuroiwa '98, Kuroiwa '00, Tomizuka, or Saffery alone or in combination (see Section IV, above).

For at least these reasons, the rejection of claims 28 and 49 under 35 U.S.C. § 103(a) is unsustainable. Therefore, applicants request reconsideration and withdrawal of the rejection.

CONCLUSION

All of the stated grounds of objection and rejection have been traversed properly or rendered moot. Thus, the present application is in condition for allowance, and applicants request an early indication to this effect. Also, Examiner Hill is invited to contact the undersigned directly, should he feel that any issue needs further consideration.

The Commissioner is hereby authorized to charge any additional fees, which may be required under 37 C.F.R. §§ 1.16-1.17, and to credit any overpayment to Deposit Account No. 19-0741. Should no proper payment accompany this response, then the Commissioner is authorized to charge the unpaid amount to the same deposit account. If any extension is required for timely acceptance of submitted papers, then applicants hereby petition for such extension under 37 C.F.R. § 1.136 and authorize payment of the relevant fee(s) from the deposit account.

Respectfully submitted,

Date 15 February 2010

By _____

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